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EXAMINER	
ANDERSON, JAMES D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,620	AU ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,32,33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,32,33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 2/18/2010, are acknowledged and entered. Claims 22, 26, and 34 have been cancelled by Applicant. Claim 35 is newly added. Claims 27-28, 32-33, and 35 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 22, 26, and 34 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 2/18/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

With regard to the 35 U.S.C. 101 rejection of claims 32-34, Applicants argue that claims 32 and 33 have been amended to remove the "offending language". The rejection of claims 32 and 33 under 35 U.S.C. 101 has been withdrawn. However, Applicants' amendments to claims 27 and 28 have necessitated a new ground of rejection under 35 U.S.C. 101. Claims 27 and 28 recite the kit of claim 35, wherein the resulting circulating plasma concentration of suramin in said patient is between about 10 and 200 μM (claim 27) or between about 10 and 50 μM. Because the claims positively recite that the "the resulting" circulating plasma concentration of suramin in said patient **is between** certain values, the claims necessarily require that the suramin is administered to a patient and that circulating plasma concentrations of suramin in the patient are measured. The claims, which depend from a product claim, thus require an active method step(s) and are therefore non-statutory. The Examiner suggests amending claims 27 and 28 to recite that the circulating plasma concentration of suramin in said patient **would be** between the recited values.

With regard to the 35 U.S.C. 112, 2nd Paragraph rejection of claims 22, 26-28, and 32-34 as lacking antecedent basis for "said chemotherapeutic agent", the rejection is moot in light of Applicants cancellation of claim 22.

With regard to the 35 U.S.C. 103 rejections of claims 22, 26-28, and 32-34, Applicants argue that new claim 35 is directed to a kit for providing personalized or individual treatment of suramin to a patient such that the printed matter breathes "life and meaning" to the substrate suramin and enables using suramin in a personalized manner. Applicants argue that such use and personalized treatment are not disclosed in Agyin. Applicants argue that claim 35 lists suramin as the only substrate in the kit and in a defined amount (or quantity), where the intended use of suramin as a personalized treatment is achieved by using the specified dosing nomogram. Applicants argue that neither Agyin, Klohs, nor Lopez disclose a product or a kit comprising a defined amount of suramin as the substrate given in accordance with the nomogram (instructions).

With regard to the cited prior art of Tu, Klohs, or Lopez, Applicant first argues that the prior art does not teach the personalized dosing nomogram or the equations of claim 35. This is not persuasive for the reasons discussed in previous Office Actions. The claimed nomogram is not given patentable weight because it merely provides instructions for administering suramin to a subject. Applicants are claiming a product, not a method of treatment.

Second, Applicant argues that the prior art teaches the **use** of suramin as a cytotoxic agent at the maximally tolerated doses that produce toxicity in patients (plasma or serum concentration of over 100 μg/mL). In response, Applicants are respectfully reminded that the prior art relied on by the Examiner is cited for their teaching, suggestion, and motivation to make a kit comprising suramin and instructions. Applicants are claiming a product (*i.e.*, a kit), not a method of administration.

Third, Applicant argues that neither Tu nor Klohs contains enablement steps to determine the suramin dose that would yield the targeted plasma concentrations. In response, Applicants are respectfully reminded that the prior art relied on by the Examiner is cited for their teaching, suggestion, and motivation to make a kit comprising suramin and instructions. Applicants are claiming a product (*i.e.*, a kit), not a method of administration.

Fourth, Applicant argues that the **method** of Tu requires using a test dose in a patient in conjunction with repeated plasma sampling and real time drug concentration analyses for approximately 7 says, whereas the instant disclosure does not require the use of a test dose and can be used to instantaneously determine the first treatment dose. In response, Applicants are respectfully reminded that the prior art relied on by the Examiner is cited for their teaching, suggestion, and motivation to make a kit comprising suramin and instructions. Applicants are claiming a product (*i.e.*, a kit), not a method of administration.

Fifth, Applicants argue that the **method** of Tu requires concentration analysis of suramin in blood samples of the patient, whereas the nomogram does not require analyzing suramin concentration in multiple blood samples from a patient in order to calculate the dose. In response, Applicants are respectfully reminded that the prior art relied on by the Examiner is cited for their teaching, suggestion, and motivation to make a kit comprising suramin and instructions. Applicants are claiming a product (*i.e.*, a kit), not a method of administration.

Sixth, Applicants argue that the prior art does not offer **personalized treatment** based on the treatment time status of an individual patient, whereas the instant disclosure accommodates changes in dosing intervals, a frequent necessity in clinical practice. In response, Applicants are respectfully reminded that the prior art relied on by the Examiner is cited for their teaching, suggestion, and motivation to make a kit comprising suramin and instructions. Applicants are claiming a product (*i.e.*, a kit), not a method of administration or method of treatment.

Applicants argue that the methods of choosing proper doses for most drugs is a relatively routine and easy task but that these methods do not apply to suramin due to its unusual pharmacokinetic characteristics. In response, Applicants are respectfully reminded that the prior art relied on by the Examiner is cited for their teaching, suggestion, and motivation to make a kit comprising suramin and instructions. Applicants are claiming a product (*i.e.*, a kit), not a method of administration, method of treatment, or method for determining a dose of suramin to be administered to a patient.

The Examiner has carefully considered Applicants' arguments but is not persuaded that Applicants' claimed kit comprising suramin and a nomogram is patentably distinct from other kits comprising suramin as suggested and motivated by the cited prior art. As has been discussed *ad nauseum* in the prosecution of the instant application (see Office Actions mailed 6/6/2007,

12/12/2007, 7/16/2008, 1/5/2009, and 10/26/2009), the contents of instructions provided in a kit are not given patentable weight in claims drawn to a product (*i.e.*, kit). It matters not what the content of the instructions is.

While Applicants may very well have discovered a novel, unobvious way of determining suitable doses of suramin to administer to a patient, the claims are not drawn to methods of determining such doses or methods of administering suramin by calculating an appropriate dose using a nomogram. The claims are **product** claims. As discussed in the previous Office Action, if the Examiner were to accept Applicants' argument that the recited nomogram should be given patentable weight, then an inventor could repeatedly patent the same kit comprising the same amount of suramin by merely changing the instructions provided with the kit. As Applicants admit in their argument discussed *supra*, the nomogram is directed to an "intended use" of the suramin present in the kit. However, the claimed nomogram has no bearing on the contents of the kit and does not limit the suramin present in the kit in any way, shape, or form. In other words, whether or not the nomogram is present in the kit, the kit still contains "not substantially in excess of about 800 mg of suramin" formulated in a pharmaceutical carrier. The nomogram merely provides instructions for how much suramin to administer to a subject.

Claim Interpretation

Claim 35 is the only independent claim presented for examination. Claim 35 recites a "kit" comprising:

(a) "not substantially in excess of about 800 mg of suramin" formulated in a pharmaceutical carrier; and

(b) a dosing nomogram to calculate the dose of suramin for a patient based on the body surface area and the timing of the treatment for said patient.

The recited nomogram delineates how suramin is *intended to be administered*, including a method of determining at what dose suramin should be administered so as to establish a low circulating dose of suramin in a patient of below about 200 μM. As such, the recited instructions merely disclose an intended use of the claimed composition and instructions for administering suramin.

Upon careful review of the claims, Applicant's previous arguments, and guidance provided in the MPEP and established case law, the Examiner is not persuaded that the claimed instructions breath "life and meaning" into the claimed composition. The instructions have no bearing whatsoever on the claimed suramin present in the composition and further do not affect the amounts of suramin present in the kit. The recited instructions would only indicate to the skilled artisan how to determine how much suramin to remove from the claimed kit and administer to a patient but do not in any way limit the amount of suramin present in the claimed kit.

As clearly set forth in the MPEP and established case law, instructions reciting an intended use or printed material not functionally related to the product are not to be given patentable weight by the Examiner when examining the patentability of compositions or kits comprising active agents. MPEP 2112.01 (III) states that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. Also see *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004) and *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983).

In this case, the recited instructions (*i.e.*, printed material) are not functionally related to the claimed kit (*i.e.*, product) because the instructions do not determine what is present in the composition or how much suramin is present in the kit. The printed material only establishes *how to administer suramin* so as to establish a low circulating dose of suramin in a patient of below about 200 μM. Contrary to Applicant's assertions, the claimed nomogram is not required to enable use of a kit comprising suramin. One skilled in the art could readily administer any known therapeutic dose of suramin to treat cancer and does not require Applicant's instructions and nomogram to do so. Applicants are respectfully reminded that the present claims are drawn to a **product**, not a method of treatment.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. This is a New Matter rejection.

The claims are drawn to a kit comprising "not substantially in excess of about 800 mg of suramin" formulated in a pharmaceutical carrier.

There is no support, either explicit or implicit, for the claimed amount of suramin. Nowhere do Applicants teach the claimed limitation of an amount of suramin "not substantially in excess of about 800 mg".

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are now drawn to a kit comprising "not substantially in excess of about 800 mg of suramin" formulated in a pharmaceutical carrier.

There is no disclosure of such an amount of suramin in the instant application.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Agyin *et al***. (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Agyin *et al*. disclose benzimidazole compounds for the treatment of cancers (Abstract; col. 2, line 39 to col. 3, line 61). The benzimidazole compounds are inhibitors of microtubules as recited in claim 22 (col. 25, lines 43-67; Table 5). The compounds of the invention are disclosed to be useful in combination therapy, such as by combining the benzimidazole compound with a chemotherapeutic agent and/or "potentiator" (col. 17, lines 1-60; col. 23, lines 29-31). A suitable potentiator is suramin as recited in claim 35 (col. 17, lines 56-57).

Agyin *et al*. disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g*., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art to formulate a kit comprising suramin as a potentiator and an anti-microtubule agent as disclosed in Agyin *et al*. for the treatment of cancer. One skilled in the art would have been motivated to additionally provide instructions for the therapeutic use of a suramin potentiator in combination with an anti-microtubule agent of Agyin *et al*. As discussed in previous Office Actions, there

must be a functional relationship between the printed matter and a substrate in order for printed material to have any patentable weight.

With regard to claims 27-28 and 32-33, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35.

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tu *et al.*** (Clinical Cancer Research, May 1998, vol. 4, pages 1193-1201) in view of **Agyin *et al.*** (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Tu *et al.* disclose that suramin combined with doxorubicin is effective in the treatment of patients with androgen-independent prostate cancer (Abstract). The authors disclose that suramin is an agent with diverse biological effects that result in tumor suppression with cytotoxic effects including activation of apoptotic cell death, inhibition of cellular energy metabolism, and inhibition of DNA and RNA polymerases, protein kinase C, and DNA topoisomerase II (page 1193, right column). The most serious toxicities of suramin are dose dependent and occur when plasma suramin levels exceed 350 μg/mL.[1] Suramin was known to have synergistic antitumor activity when combined with doxorubicin (page 1193, right column). Doxorubicin is an antitumor antibiotic whose mechanism of action is believed to involve the formation of free radicals and the inhibition of topoisomerase II, causing DNA damage (*id.*).

The authors provide instructions for administering suramin and doxorubicin to patients to treat prostate cancer and provide measurements of suramin plasma concentrations (pages 1194-1195; Table 3). Tu *et al.* specifically disclose adjusting suramin doses proportionately based on assessment of steady-state plasma concentrations of suramin (page 1194, right column). As seen

[1] The molecular weight of suramin is 1429.21 g/mol. 350 μg/mL is equivalent to about 245 μM.

in Table 3, the circulating plasma concentrations of suramin are below about 200 μM as recited in the instantly claimed instructions. In fact, the authors disclose that single-agent suramin has a narrow clinical therapeutic index of 150 to 250 μg/mL (page 1199, left column). 150 to 250 μg/mL suramin is equivalent to 105 to 175 μM suramin, which is below the amount recited in the claimed instructions.

The authors conclude that the results from this study could be used to develop future clinical studies of suramin combined with other chemotherapeutic agents in the treatment of prostate cancer and that long-term exposure to suramin at lower concentrations and in combination with other chemotherapeutic agents should be explored. The authors explicitly suggest a fixed dosing scheme targeting a suramin concentration of 200 μg/mL (*i.e.*, 140 μM) for future suramin combination studies (page 1200, right column).

Tu *et al.* differ from the instant claims in that they do not explicitly disclose a "kit" comprising suramin and doxorubicin and instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. For example, Agyin *et al.* disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and doxorubicin as suggested and motivated by Tu *et al.* for use in the treatment of prostate cancer. Using the disclosure of Tu et al. as a guide, the skilled artisan could readily provide instructions for administering suramin and doxorubicin to treat prostate cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Tu *et al.* disclose that single-agent suramin has a narrow clinical therapeutic index of 150 to 250 μg/mL (*i.e.*, 105 to 175 μM) and explicitly suggest a fixed dosing scheme targeting a suramin concentration of 200

μg/mL (*i.e.*, 140 μM). Agyin *et al.* disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-33, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35. Regardless of this fact, as discussed above, Tu et al. provide guidance and direction to administer suramin in such a way so as to provide a circulating concentration of suramin below 200 μM.

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Klohs *et al.*** (USP No. 5,597,830; Issued Jan. 28, 1997) in view of **Agyin *et al.*** (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Klohs et al. disclose suramin in combination with a vinca alkaloid or estramustine is synergistic for treating cancer (Abstract). Compositions for use in the invention consist essentially of suramin and a vinca alkaloid or estramustine together with common excipients, diluents, and carriers (col. 1, line 65 to col. 2, line 10). Suramin is disclosed to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a combination comprising each active ingredient packaged separately, wherein the individually packaged drugs can be placed in a single carton, thereby providing convenience to the attending physician or medical attendant (*i.e.*, a kit) (col. 4, lines 39-44).

Klohs *et al.* differ from the instant claims in that they do not explicitly disclose a kit comprising suramin and a vinca alkaloid or estramustine and instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. Klohs *et al.* disclose that kits comprising the individual active agents provide convenience to physicians or medical attendants. Agyin *et al.* disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and a vinca alkaloid or estramustine as suggested and motivated by Klohs *et al.* for use in the treatment of cancer. Using the disclosure of Klohs *et al.* as a guide, the skilled artisan could readily provide instructions for administering suramin and a vinca alkaloid or estramustine to treat cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Klohs *et al.* disclose that suramin is to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a kit comprising each active ingredient packaged separately wherein the individual packages can be placed in a single carton. Agyin *et al.* disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-34, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not

provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach *how* to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35. Regardless of this fact, as discussed above, Klohs et al. provide guidance and direction to administer suramin in such a way so as to provide suramin plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM).

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lopez *et al.*** (European Journal of Cancer, 1994, vol. 30A, no. 10, pages 1545-1549) in view of **Klohs *et al.*** (USP No. 5,597,830; Issued Jan. 28, 1997) and **Agyin *et al.*** (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Lopez *et al.* disclose that suramin has shown antitumor activity *in vitro* and *in vivo* and that at plasma levels higher than 200 μM there is excessive toxicity (Abstract). Lopez *et al.* sought to improve the antitumor effects of suramin by combining it with several other antitumor agents. In this regard, the authors demonstrate that suramin in combination with doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor resulted in synergistic growth inhibition of breast and/or prostate cancer cells (Abstract; Table 2).

The instant claims differ from Lopez *et al.* in that the primary reference does not disclose kits comprising suramin.

However, Klohs *et al.* disclose suramin in combination with a vinca alkaloid or estramustine is synergistic for treating cancer (Abstract). Suramin is disclosed to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a combination comprising each active ingredient packaged separately, wherein the individually packaged drugs can be placed in a single carton, thereby providing convenience to the attending physician or medical attendant (*i.e.*, a kit) (col. 4, lines 39-44).

The instant claims differ from Klohs *et al.* in that the secondary reference does not teach kits with instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. Klohs *et al.* disclose that kits comprising the individual active agents (*e.g.*, suramin and a cytotoxic agent) provide convenience to physicians or medical attendants. Agyin *et al.* disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor as suggested and motivated by Lopez *et al.* in view of Klohs *et al.* for use in the treatment of cancer. Using the disclosures of Lopez *et al.* and Klohs *et al.* as a guide, the skilled artisan could readily provide instructions for administering suramin and doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor to treat cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Lopez et al. teach that plasma levels above 200 μM, suramin results in "excessive toxicity", thus motivating one skilled in the art to administer suramin in doses so as not to exceed a plasma level above 200 μM. Klohs *et al.* provide such guidance, disclosing that suramin is to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). Klohs *et al.* disclose a kit comprising each active ingredient packaged separately wherein the individual packages can be placed in a single carton. The skilled artisan could readily and routinely modify the kits of Klohs et al. so as to provide kits comprising suramin and other cytotoxic agents, such as doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor as suggested and motivated by Lopez *et al.*

Agyin *et al.* disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-33, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach *how* to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35. Regardless of this fact, as discussed above, both Lopez *et al.* and Klohs *et al.* provide guidance and direction to administer suramin in such a way so as to provide suramin plasma levels of below about 200 μM (Lopez *et al.*) or about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (Klohs *et al.*).

Regarding the above rejections under 35 U.S.C. 103, it is noted that the MPEP and established case law supports the rejection of pharmaceutical kits that differ from the prior art only in the content of the provided instructions. The following section of the M.P.E.P., as noted by Applicants in their response filed 9/10/2007 (page 7) is deemed relevant to the present claims:

> "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004) (Claim at issue was a kit requiring instructions and a buffer agent. The Federal Circuit held that the claim was anticipated by a prior art reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.). See also *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983) ("Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability .... [T]he critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate.")." M.P.E.P. § 2112.01

The decision in *Gulack* held that there must be a functional relationship between the printed matter and a substrate in order for printed material to have any patentable weight. However, in *Ngai*, the court distinguished claims directed to a kit comprising instructions and a buffer (more closely related to the present case) from the printed band and instructions at issue in *Gulack*. There the printed matter and the circularity of the band were interrelated, so as to produce a new product useful for "educational and recreational mathematical" purposes. In *Ngai*, addition of a new set of instructions into a known kit was held to not interrelate with the kit in the same way as the numbers interrelated with the band. In *Gulack*, the printed matter would not achieve its educational purposes without the band, and the band without the printed matter would similarly be unable to produce the desired result. In the present case, the printed matter in no way depends on the kit (*i.e.*, a kit containing suramin formulated in a pharmaceutical carrier), and the kit does not depend on the printed matter (*i.e.*, instructions for administering suramin). All that the printed matter does is teach a method of administering an obvious product. As the court stated in *Ngai*, "If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. This was not envisioned by *Gulack*. Ngai is entitled to patent his invention of a new RNA extraction method, and the claims covering that invention were properly allowed. He is not, however, entitled to patent a known product by simply attaching a set of instructions to that product." (Emphasis added).

In the instant case, the cited prior art clearly teaches, suggests, and motivates one skilled in the art to formulate pharmaceutical compositions and kits comprising suramin and other cytotoxic agents for the treatment of cancer. It was clearly known in the art that suramin has antitumor activity, is synergistic when combined with other chemotherapeutic agents, and results in excessive toxicity when plasma levels of suramin are greater than 200 μM. As such, it would be obvious to one skilled in the art to formulate suramin in a kit with other cytotoxic agents, especially those which were known to be synergistic when administered with suramin, and to provide instructions for treating cancer with the active agents in the kit. It would further have been obvious to the skilled artisan to instruct those administering suramin not to administer doses that result in plasma concentrations above 200 μM which cause excessive toxicity. As discussed

above, the claimed instructions do not control what is in the kit. Put another way, the recited instructions have no bearing and place no limitations on the components of the kit, the content of the kit, or the amounts of active agents in the kit. The kit, in and of itself, stands alone and does not require the claimed instructions to "breath life and meaning" into the kit. Rather, the instructions only tell one skilled in the art *how to administer* the components of the kit in a particular manner. As such, there is not a functional relationship between the instructions and the claimed kit.

There can be no doubt that the skilled artisan could administer suramin and a cytotoxic agent in a manner distinct from that disclosed in Applicant's recited instructions. However, even such a distinct administration method does not change the contents of the kit or the amounts of active agents present in the kit.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Primary Examiner, Art Unit 1614

April 14, 2010